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Appendix 9: BMD Analysis of Brain Cholinesterase Inhibition Data

Dimethoate: Issues Related to the Hazard and Dose Response Assessment Analysis of variance (ANOVA) is typically used to identify statistically significant difference between various dose groups within a toxicity study. Although the group means and standard deviations can be used to characterize the response of the experimental dose groups, ANOVA does not characterize the dose-response relationship. Benchmark dose (BMD) analysis attempts to model the dose-response relationship with a dose-response curve that can be described by a mathematical function. The dose-response curve which is estimated based on the experimental observations interpolates the magnitude of the response for any dose within the experimental dosing range. Various mathematical models can be used to model this dose-response curve. Once a BMD model has been selected, the dose resulting in a specified response (i.e. benchmark response, BMR) is determined. The BMR is expressed as certain percent change in the control group response (i.e., background). The dose resulting in the BMR is termed the "benchmark dose". Generally, the dose resulting in a BMR of X% is referred to as the BMD_X. The corresponding lower 95% confidence limit on the BMD_X is the BMDL_X.

A BMD analysis of the brain cholinesterase inhibition (ChEI) data from various dimethoate studies was performed using EPA's OPCumRisk program. The exponential function used for modeling the effect of dimethoate on cholinesterase activity (ChE) was:

$$y = B + (A - B) \times e^{-m*dose}$$

where y is cholinesterase activity, dose is the dose of dimethoate, in mg/kg/day, m is the dose scale factor, A is background cholinesterase activity, and B is the limiting highdose ChE activity. Both y (cholinesterase activity) and dose were extracted from the oral toxicity studies. The equation for the exponential model reflects the observation that cholinesterase activity decreases to a limiting value (B) as dose increases. The model has three parameters to be estimated: m (dose scale factor), A (background), and B (limiting high-dose ChE activity). The OPCumRisk program can be obtained at www.epa.gov/pesticides/cumulative/EPA approach methods.htm. OPCumRisk utilizes the same dose-response model (i.e., exponential model) as utilized in the Preliminary OP Cumulative Risk Assessment (CRA). This method has been previously evaluated by the FIFRA SAP (2001, 2002). For the final OP CRA, the exponential model was expanded to include a "low dose shoulder." The low dose shoulder corresponds to a part of the dose-response curve where the response of the low dose group is similar to that of the control group. However, for the OP CRA there was no evidence of low dose shoulder for dimethoate. Similar to the observations of the OP CRA, the brain ChEI data from the studies evaluated here do not suggest the need to model a low dose shoulder.

The calculated BMD values represent the dose at which a 10% reduction in

cholinesterase activity compared to background activity is expected. For each brain ChE data set, parameters were estimated including all dose groups. The OPCumRisk program utilizes a decision algorithm for choosing the appropriate options for the exponential model. Generally the model is fitted until an adequate p-value for the χ^2 goodness of fit (GoF) is obtained. The decision algorithm is provided below.

- 1. If the p-value for the GoF statistic is greater than 0.05, then the model's fit was considered adequate and the parameter estimates were used.
- 2. Otherwise (that is, if the p-value was less than 0.05, or no estimates resulted because the model did not converge), the horizontal asymptote was set to zero and the model was refit to the data.
- 3. If the p-value was still less than 0.05, or there was no model fit at all, then the highest dose was dropped and the model was refit with the horizontal asymptote set to zero until either the p-value exceeded 0.05, or there are only three doses remaining.

Although the user can specify options not consistent with default decision algorithm utilized by OPCumRisk, all BMD values provided in OPP's current analysis are based on the default decision algorithm. The decision algorithm and technical details of the "basic" exponential model used in this BMD analysis can be obtained at www.epa.gov/scipoly/sap/2001/september/rpfappendix1.pdf.

Tables A9.1 and A9.2 contain summary information of the OPCumRisk model runs for the comparative ChEI (gavage) study, the DNT (gavage) range-finding study, the one-generation dietary range-finding reproductive toxicity study, two two-generation dietary reproductive toxicity studies, and a 28-day dietary toxicity study.

Clear dose-response relationships were exhibited by a majority of the brain ChEI data from repeated dosing and adequate model fits were attained for most of the data sets. The GoF statistic for the day 28 adult females from the 28-day dietary study and the PND 42 males from one-generation reproductive toxicity study result in highly significant p-values (i.e. < 0.01) indicating the model's lack of fit. For the day 28 females, the brain ChE levels of the low dose group were higher than those of the control group. For the PND 42 males, although the brain ChE levels of the medium dose group were higher than the model estimates, visually the fit of the model seems reasonable. Additionally, the GoF statistic for the day 218 adult females from the "new" two-generation reproductive toxicity study has a borderline significant p-value of 0.057 indicating the fit of the model is questionable. All BMD values were within their respective experimental dose ranges except for the PND 4 groups from the comparative ChEI study.

For the data sets providing adequate fits and BMD estimates within their

experimental dose ranges, the BMD_{10} and $BMDL_{10}$ values are consistent across sex and age for all studies. The text and graphical output from the OPCumRisk model are included at the end of this appendix. The output files are identified by the subpopulation, sex, and MRID number of the corresponding data sets.

Day 11 Adults : Female : 45529702

DIMETHOATE:11-D:BRAIN:F:WHOLE
Wed Aug 18 18:39:56 2004
MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 546.8830 551.2802 -270.4415

```
Coefficients:
```

Value Std.Error A 1.467991e+04 331.88894597 m 2.875262e-01 0.01490362

Correlation:

A 1.0000000 0.5903737 m 0.5903737 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.401751e+04 1.467991e+04 1.537360e+04 m 2.586446e-01 2.875262e-01 3.196329e-01

Residual standard error: lower est. upper 1225.850 1534.016 2050.478

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.7123 with 2 degrees of freedom. P = 0.7

```
dose n chei Expected sd Exp.SD X2 Resid.
1 0.0 8 14868.75 14679.905 1399.7289 1513.3442 0.35294916
2 0.1 8 13912.50 14263.830 446.2142 1470.6675 -0.67568682
3 0.5 8 12881.25 12714.161 845.1278 1311.6610 0.36030474
4 3.0 8 6187.50 6195.981 1077.6131 641.5657 -0.03738933
```

BMD = 0.3664: BMDL = 0.3377

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2875

se: 0.0149

var=se^2: 0.0002221

Per cent. of background at unit dose: 75

Per cent. of background at the highest dose: 42

ED50 (95% CI): 2.411 (2.178 , 2.669)

ln(Potency) -1.246

se[log(Potency)]: 0.05183
se[log(Potency)]^2: 0.002687

Day 11 Adults : Male : 45529702

DIMETHOATE:11-D:BRAIN:M:WHOLE Wed Aug 18 18:40:01 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 580.8117 586.6747 -286.4059

Coefficients:

Value Std.Error A 1.418582e+04 6.693422e+02 B 6.934757e+02 2.463564e+04

m 2.295838e-01 6.112029e-01

Correlation:

A B m A 1.0000000 0.6252848 0.6441556 B 0.6252848 1.0000000 0.9990744 m 0.6441556 0.9990744 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.288084e+04 1.418582e+04 1.562301e+04 B 1.935073e-29 6.934757e+02 2.485221e+34 m 9.914506e-04 2.295838e-01 5.316323e+01

Residual standard error: lower est. upper 1881.485 2362.467 3175.900

Degrees of freedom: 32 total; 29 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.02856 with 1 degrees of freedom. P = 0.866

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 8 14100.00 14185.82 529.1503 2376.373 -0.102149399

2 0.1 8 13987.50 13879.59 661.5728 2325.356 0.131255835

3 0.5 8 12700.00 12722.60 547.7226 2132.402 -0.029977672

4 3.0 8 7468.75 7469.37 2484.3708 1251.247 -0.001401282
```

BMD = 0.4839: BMDL = 0.2183

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2296 se: 0.6112

var=se^2: 0.3736

Per cent. of background at unit dose: 79

Per cent. of background at the highest dose: 50

ED50 (95% CI): 3.019 (0.01636 , 557.2)

ln(Potency) -1.471
se[log(Potency)]: 2.662
se[log(Potency)]^2: 7.087

GD 20 Dams : Female : 45529702

DIMETHOATE:15-D:BRAIN:F:WHOLE
Thu Sep 09 15:28:34 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 546.7020 551.0992 -270.3510

Coefficients:

Value Std.Error A 1.326628e+04 338.81486611 m 3.176544e-01 0.01701312

Correlation:

A 1.0000000 0.5864056 m 0.5864056 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.259207e+04 1.326628e+04 1.397660e+04 m 2.847418e-01 3.176544e-01 3.543713e-01

Residual standard error: lower est. upper 1216.627 1522.473 2035.049

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.034 with 2 degrees of freedom. P = 0.596

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 8 12837.50 13266.284 1372.6278 1543.4002 -0.7857879

```
2 0.1 8 13043.75 12851.498 530.1196 1496.1318 0.3634514
3 0.5 8 11562.50 11318.048 299.7022 1321.0981 0.5233637
4 3.0 8 5093.75 5115.436 1080.8190 607.0403 -0.1010440
```

BMD Computation

BMD = 0.3317: BMDL = 0.3048

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3177 se: 0.01701

var=se^2: 0.0002894

Per cent. of background at unit dose: 73

Per cent. of background at the highest dose: 39

ED50 (95% CI): 2.182 (1.965 , 2.424)

ln(Potency) -1.147

se[log(Potency)]: 0.05356
se[log(Potency)]^2: 0.002869

GD 20 Fetuses : Both : 45529702

DIMETHOATE:15-D:PLASMA:F:WHOLE Wed Aug 18 19:36:13 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 424.5588 428.9560 -209.2794

Coefficients:

Value Std.Error A 1689.2787183 42.19501281 m 0.1178956 0.01639579

Correlation:

A 1.0000000 0.5920042 m 0.5920042 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1605.2660561 1689.2787183 1777.6882389 m 0.0887461 0.1178956 0.1566195

Residual standard error: lower est. upper 162.1117 202.8648 271.1640

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 4.084 with 2 degrees of freedom. P = 0.130

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 8 1781.25 1689.279 175.1275 192.4780 1.3515001

```
2 0.1 8 1568.75 1669.480 173.0762 190.2102 -1.4978530
3 0.5 8 1600.00 1592.578 136.2770 181.4030 0.1157292
4 3.0 8 1187.50 1186.034 164.2081 134.8841 0.0307423
```

BMD Computation

BMD = 0.8937: BMDL = 0.7273

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1179

se: 0.0164

var=se^2: 0.0002688

Per cent. of background at unit dose: 89

Per cent. of background at the highest dose: 70

ED50 (95% CI): 5.879 (4.477 , 7.722)

ln(Potency) -2.138

se[log(Potency)]: 0.1391
se[log(Potency)]^2: 0.01934

PND 4 Offspring: Female: 45529702

DIMETHOATE: 0-D:BRAIN:F:WHOLE Thu Aug 19 14:59:15 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 424.0659 428.2695 -209.0329

Coefficients:

Value Std.Error A 2.811752e+03 62.14188020 m 2.335455e-02 0.01407783

Correlation:

A m A 1.0000000 0.6016185 m 0.6016185 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 2.687299e+03 2.811752e+03 2.941969e+03 m 6.793986e-03 2.335455e-02 8.028202e-02

Residual standard error: lower est. upper 225.6483 284.3424 384.5593

Degrees of freedom: 30 total; 28 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 4.182 with 2 degrees of freedom. P = 0.124

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 7 2785.714 2811.752 299.9504 271.9717 -0.2532981

BMD Computation

BMD = 4.511: BMDL = 2.265

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.02335

se: 0.01408

var=se^2: 0.0001982

Per cent. of background at unit dose: 98

Per cent. of background at the highest dose: 93

ED50 (95% CI): 29.68 (9.106 , 96.73)

ln(Potency) -3.757

se[log(Potency)]: 0.6028
se[log(Potency)]^2: 0.3634

PND 4 Offspring: Male: 45529702

DIMETHOATE: 0-D:BRAIN: M:WHOLE Thu Aug 19 14:59:20 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 497.8960 502.5621 -245.9480

Coefficients:

Value Std.Error A 2.968973e+03 60.11820162 m 2.476742e-02 0.01313410

Correlation:

A 1.0000000 0.5899821 m 0.5899821 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 2.849146e+03 2.968973e+03 3.093838e+03 m 8.420172e-03 2.476742e-02 7.285183e-02

Residual standard error: lower est. upper 243.4088 301.7801 397.2265

Degrees of freedom: 35 total; 33 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 5.049 with 2 degrees of freedom. P = 0.0801

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 10 3120.000 2968.973 242.6131 287.2535 1.6626109

```
2 0.1 8 2825.000 2961.628 219.5775 286.5337 -1.3486827
3 0.5 8 2865.625 2932.432 225.1735 283.6723 -0.6661198
4 3.0 9 2769.444 2756.367 339.7558 266.4247 0.1472493
```

BMD Computation

BMD = 4.254: BMDL = 2.272

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.02477

se: 0.01313

var=se^2: 0.0001725

Per cent. of background at unit dose: 98

Per cent. of background at the highest dose: 93

ED50 (95% CI): 27.99 (9.898 , 79.13)

ln(Potency) -3.698

se[log(Potency)]: 0.5303
se[log(Potency)]^2: 0.2812

PND 21 Offspring: Female: 45529702

DIMETHOATE:11-D:BRAIN:F:WHOLE Wed Aug 18 20:12:24 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 517.114 522.977 -254.557

Coefficients:

Value Std.Error
A 1.023172e+04 244.4269786
B 4.761725e+03 1434.4099641
m 5.070756e-01 0.3102889

Correlation:

A B m A 1.0000000 0.5727942 0.6245823 B 0.5727942 1.0000000 0.9863055 m 0.6245823 0.9863055 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 9743.8245469 1.023172e+04 10744.040990 B 2571.5535403 4.761725e+03 8817.247872 m 0.1450599 5.070756e-01 1.772549

Residual standard error:

lower est. upper 689.2430 865.4407 1163.4250

Degrees of freedom: 32 total; 29 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.05658 with 1 degrees of freedom. P = 0.812

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 8 10275.00 10231.718 376.0699 861.9491 0.142027400

2 0.1 8 9906.25 9961.263 313.3204 839.0650 -0.185444384

3 0.5 8 9018.75 9006.715 247.7578 758.3745 0.044884938

4 3.0 8 5956.25 5956.611 964.8973 501.7452 -0.002033078
```

BMD = 0.4084: BMDL = 0.2609

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5071 se: 0.3103

var=se^2: 0.09628

Per cent. of background at unit dose: 60

Per cent. of background at the highest dose: 22

ED50 (95% CI): 1.367 (0.412 , 4.536)

ln(Potency) -0.6791
se[log(Potency)]: 0.6119
se[log(Potency)]^2: 0.3744

PND 21 Offspring : Male : 45529702

DIMETHOATE:11-D:BRAIN:M:WHOLE Wed Aug 18 20:12:31 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 490.4541 496.3170 -241.2270

Coefficients:

Value Std.Error
A 1.030886e+04 163.3439882
B 4.209439e+03 1128.3793005
m 4.723459e-01 0.1929238

Correlation:

A B m A 1.0000000 0.5845660 0.6296056 B 0.5845660 1.0000000 0.9903008 m 0.6296056 0.9903008 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper
A 9980.1364087 1.030886e+04 10648.405296
B 2432.9062934 4.209439e+03 7283.213837
m 0.2048675 4.723459e-01 1.089049

Residual standard error: lower est. upper 462.2901 580.4697 780.3343

Degrees of freedom: 32 total; 29 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2933 with 1 degrees of freedom. P = 0.588

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 8 10375.00 10308.857 207.0197 576.9300 0.324268111

2 0.1 8 9943.75 10027.452 331.0562 561.0777 -0.421947102

3 0.5 8 9043.75 9025.808 339.5769 504.7310 0.100541175

4 3.0 8 5687.50 5688.128 566.7892 318.2699 -0.005577083
```

BMD = 0.392: BMDL = 0.2888

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.4723 se: 0.1929

var=se^2: 0.03722

Per cent. of background at unit dose: 62

Per cent. of background at the highest dose: 24

ED50 (95% CI): 1.467 (0.659 , 3.268)

ln(Potency) -0.75

se[log(Potency)]: 0.4084
se[log(Potency)]^2: 0.1668

GD 20 Dams : Female : 45529701

DIMETHOATE:15-D:BRAIN:F:WHOLE
Thu Sep 09 15:28:26 2004

MRID: 45529701 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 316.7494 320.7324 -154.3747

Coefficients:

Value Std.Error
A 1.337673e+04 489.4951784
B 1.239493e+03 135.0241940
m 5.968458e-01 0.0463716

Correlation:

A B m A 1.0000000 0.2136947 0.4272598 B 0.2136947 1.0000000 0.8419012 m 0.4272598 0.8419012 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.238285e+04 1.337673e+04 1.445039e+04 B 9.849838e+02 1.239493e+03 1.559765e+03 m 5.066082e-01 5.968458e-01 7.031567e-01

Residual standard error: lower est. upper 1058.068 1410.028 2113.835

Degrees of freedom: 20 total; 17 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.307 with 1 degrees of freedom. P = 0.129

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 5 12710 13376.732 1333.8853 1470.2133 -1.01404205

2 0.2 5 12680 12011.051 640.8978 1334.3441 1.12101123

3 3.0 5 3240 3264.840 411.4000 386.4720 -0.14372031

4 6.0 5 1580 1577.464 195.5761 160.4225 0.03535067
```

BMD = 0.1956: BMDL = 0.1755

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5968 se: 0.04637

var=se^2: 0.00215

Per cent. of background at unit dose: 55

Per cent. of background at the highest dose: 2.8

ED50 (95% CI): 1.161 (0.9973 , 1.352)

ln(Potency) -0.5161

se[log(Potency)]: 0.07769
se[log(Potency)]^2: 0.006036

GD 20 Fetuses : Female : 45529701

DIMETHOATE:15-D:BRAIN:F:WHOLE
Thu Aug 19 20:06:58 2004

MRID: 45529701 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 319.4744 323.4574 -155.7372

Coefficients:

Value Std.Error
A 2053.1677722 264.4939877
B 355.9855520 4201.6221520
m 0.1290254 0.4747553

Correlation:

A B m A 1.0000000 0.3581436 0.4168177 B 0.3581436 1.0000000 0.9949052 m 0.4168177 0.9949052 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper
A 1.564541e+03 2053.1677722 2.694399e+03
B 5.454544e-09 355.9855520 2.323305e+13
m 5.484962e-05 0.1290254 3.035127e+02

Residual standard error:

lower est. upper 610.5789 813.6847 1219.8306

Degrees of freedom: 20 total; 17 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1228 with 1 degrees of freedom. P = 0.726

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 5 1970 2053.168 288.5308 794.6247 -0.234033477

2 0.2 5 2100 2009.932 871.7798 778.4200 0.258726599

3 3.0 5 1500 1508.439 500.0000 586.8601 -0.032154703

4 6.0 5 1140 1138.547 638.7488 440.0132 0.007384745
```

BMD = 0.9994: BMDL = 0.3558

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.129 se: 0.4748

var=se^2: 0.2254

Per cent. of background at unit dose: 88

Per cent. of background at the highest dose: 46

ED50 (95% CI): 5.372 (0.003963 , 7282)

ln(Potency) -2.048
se[log(Potency)]: 3.68
se[log(Potency)]^2: 13.54

GD 20 Fetuses : Male : 45529701

DIMETHOATE:15-D:BRAIN:M:WHOLE
Thu Aug 19 20:07:03 2004

MRID: 45529701 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 322.9258 326.9087 -157.4629

Coefficients:

Value Std.Error A 2255.4458807 281.9229830 B 1067.4879280 1662.2545211 m 0.2189783 0.5838925

Correlation:

A B m
A 1.0000000 0.2889127 0.3756791
B 0.2889127 1.0000000 0.9821411
m 0.3756791 0.9821411 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper
A 1.732608e+03 2255.4458807 2936.05657
B 3.995417e+01 1067.4879280 28520.93850
m 7.892081e-04 0.2189783 60.75899

Residual standard error:

lower est. upper 649.9931 866.2098 1298.5732

Degrees of freedom: 20 total; 17 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.1795 with 1 degrees of freedom. P = 0.672

```
dose n chei Expected sd Exp.SD
                                         X2 Resid.
1 0.0 5 2150 2255.446 562.3611 840.8655 -0.28040649
2 0.2 5 2320 2204.541 675.0926 822.7411 0.31379672
3 3.0 5 1670 1683.370 564.1365 631.7107 -0.04732752
4 6.0 5 1390 1386.785 780.5447 516.1310 0.01392921
                            BMD Computation
                     BMD = 0.9615: BMDL = 0.3167
                            Potency Measures
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity
Potency: 0.219
se: 0.5839
var=se^2: 0.3409
Per cent. of background at unit dose: 80
Per cent. of background at the highest dose: 27
ED50 (95% CI): 3.165 ( 0.01701 , 589 )
ln(Potency) -1.519
se[log(Potency)]: 2.666
se[log(Potency)]^2: 7.11
                 PND 21 Offspring: Female: 45529701
                      DIMETHOATE: 11-D: BRAIN: F: WHOLE
                        Thu Aug 19 19:00:10 2004
                MRID: 45529701
                                 Guideline: NONGUIDELINE
                Continuous Exponential Model (Decreasing)
                Formula: chei = B + (A-B)*exp(-(m*dose)*g)
Variance Function: power
   The BMD corresponds to a dose that results in a 10% reduction in the
                    response relative to the control
                     Summary of Model Fitting Results
     AIC
               BIC
                      logLik
 622.9066 629.2406 -307.4533
Coefficients:
        Value
                Std.Error
A 9766.4268328 4.636244e+02
B 858.6043070 1.959891e+03
  0.2210332 9.820677e-02
```

ln(Potency) -1.509

```
Correlation:
                   В
A 1.0000000 0.3363009 0.4330857
B 0.3363009 1.0000000 0.9845464
m 0.4330857 0.9845464 1.0000000
Approximate 95% confidence intervals
 Coefficients:
         lower
                       est.
A 8.867294e+03 9766.4268328 1.075673e+04
B 8.258369e+00 858.6043070 8.926718e+04
m 8.951104e-02
                0.2210332 5.458062e-01
Residual standard error:
            est.
1579.441 1958.203 2577.539
Degrees of freedom: 36 total; 33 residual
                             Goodness of Fit
The chi-squared goodness-of-fit values should be taken as general
indications of fit only. P-values are likely to be inaccurate to some
degree
Pearson Chi-Square Statistic: 1.169 with 1 degrees of freedom. P =
              chei Expected
 dose n
                                   sd
                                        Exp.SD
                                                 X2 Resid.
1 \quad 0.0 \ 10 \ 9337.500 \ 9766.427 \ 2774.8936 \ 1929.595 \ -0.70293800
2 0.2 9 9886.111 9381.219 406.7998 1856.751 0.81576691
3 3.0 9 5413.889 5448.376 666.6276 1091.566 -0.09478175
4 6.0 8 3228.125 3223.492 749.5758 631.870 0.02073769
                             BMD Computation
                      BMD = 0.5254: BMDL = 0.3853
                             Potency Measures
A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background
activity
Potency: 0.221
se: 0.09821
var=se^2: 0.009645
Per cent. of background at unit dose: 80
Per cent. of background at the highest dose: 27
ED50 (95% CI): 3.136 ( 1.313 , 7.492 )
```

30

se[log(Potency)]: 0.4443
se[log(Potency)]^2: 0.1974

PND 21 Offspring : Male : 45529701

DIMETHOATE:11-D:BRAIN:M:WHOLE
Thu Aug 19 19:00:15 2004

MRID: 45529701 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 626.3808 632.7149 -309.1904

Coefficients:

Value Std.Error A 1.052178e+04 466.9239984 B 4.149907e+03 651.4008126 m 4.434059e-01 0.1504221

Correlation:

A B m A 1.0000000 0.1936634 0.3376864 B 0.1936634 1.0000000 0.9055094 m 0.3376864 0.9055094 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 9613.4410869 1.052178e+04 1.151595e+04 B 3015.4017893 4.149907e+03 5.711256e+03 m 0.2223587 4.434059e-01 8.841967e-01

Residual standard error: lower est. upper 1550.098 1921.824 2529.654

Degrees of freedom: 36 total; 33 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.007399 with 1 degrees of freedom. P = 0.931

```
      dose n
      chei
      Expected
      sd
      Exp.SD
      X2 Resid.

      1 0.0 10 10555.000 10521.783
      529.3864 1916.438 0.054810535

      2 0.2 9 9941.667 9981.048 542.7073 1817.253 -0.065013233

      3 3.0 9 5838.889 5834.757 695.1968 1060.878 0.011684947

      4 6.0 8 4593.750 4595.415 1680.0696 837.690 -0.005620692
```

BMD = 0.407: BMDL = 0.2863

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.4434 se: 0.1504

var=se^2: 0.02263

Per cent. of background at unit dose: 64
Per cent. of background at the highest dose: 7

ED50 (95% CI): 1.563 (0.804 , 3.039)

ln(Potency) -0.8133
se[log(Potency)]: 0.3392
se[log(Potency)]^2: 0.1151

Day 91 Adults : Female : 46348201

DIMETHOATE:91-D:BRAIN:F:WHOLE
Thu Sep 09 14:20:57 2004
MRID: 46348201 Guideline: UNKNOWN
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 54.72549 61.48101 -23.36275

Coefficients:

Value Std.Error

A 7.8579481 0.2862688

В 1.9987050 0.3001868

m 0.3008430 0.0466104

Correlation:

A B n

A 1.0000000 0.2039435 0.3840336

B 0.2039435 1.0000000 0.9507256

m 0.3840336 0.9507256 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 7.2988029 7.8579481 8.4599282

В 1.4743015 1.9987050 2.7096370

m 0.2197884 0.3008430 0.4117894

Residual standard error:

lower est. upper

 $0.7400548 \ 0.9077489 \ 1.1743976$

Degrees of freedom: 40 total; 37 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.909 with 1 degrees of freedom. P = 0.088

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 10 7.89 7.857948 0.596 0.9072286 0.1117215

2 3.9 10 3.70 3.811251 0.578 0.4340145 -0.8105887

3 5.8 10 3.17 3.022105 0.281 0.3469903 1.3478290

4 7.5 10 2.55 2.612372 0.292 0.3032918 -0.6503265
```

BMD = 0.4787: BMDL = 0.4049

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3008 se: 0.04661

var=se^2: 0.002173

Per cent. of background at unit dose: 74

Per cent. of background at the highest dose: 10

ED50 (95% CI): 2.304 (1.701 , 3.122)

ln(Potency) -1.201

se[log(Potency)]: 0.1549
se[log(Potency)]^2: 0.024

Day 91 Adults : Male : 46348201

DIMETHOATE:91-D:BRAIN:M:WHOLE
Thu Sep 09 14:21:03 2004
MRID: 46348201 Guideline: UNKNOWN
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 101.94088 108.69639 -46.97044

Coefficients:

Value Std.Error

A 7.4512046 0.4355370

B 3.0457078 0.3864785

m 0.4636045 0.1428526

Correlation:

A B r

A 1.0000000 0.1296738 0.3035647

B 0.1296738 1.0000000 0.9168315

m 0.3035647 0.9168315 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 6.6189777 7.4512046 8.3880703

B 2.3551961 3.0457078 3.9386682

m 0.2483135 0.4636045 0.8655557

Residual standard error:

lower est. upper

1.124437 1.379231 1.784376

Degrees of freedom: 40 total; 37 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.002618 with 1 degrees of freedom. P = 0.96

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 10 7.45 7.451205 0.487 1.3792849 -0.002761755

2 2.9 10 4.20 4.194143 1.048 0.7767216 0.023847433

3 4.4 10 3.61 3.618629 0.859 0.6699690 -0.040729921

4 6.1 10 3.31 3.306212 0.442 0.6119191 0.019573228
```

BMD = 0.3997: BMDL = 0.2856

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.4636 se: 0.1429

var=se^2: 0.02041

Per cent. of background at unit dose: 63

Per cent. of background at the highest dose: 5.9

ED50 (95% CI): 1.495 (0.8173 , 2.735)

ln(Potency) -0.7687
se[log(Potency)]: 0.3081
se[log(Potency)]^2: 0.09495

PND 42 Offspring: Female: 46348201

DIMETHOATE:21-D:BRAIN:F:WHOLE
Thu Sep 09 14:28:36 2004
MRID: 46348201 Guideline: UNKNOWN
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 175.16891 184.69701 -83.58445

Coefficients:

Value Std.Error

A 7.6003104 0.36099304

В 1.7805163 0.21347974

m 0.3878520 0.05812968

Correlation:

A B r

A 1.0000000 0.1525420 0.3487570

B 0.1525420 1.0000000 0.9196862 m 0.3487570 0.9196862 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 6.9144277 7.6003104 8.3542299

в 1.4023601 1.7805163 2.2606449

m 0.2877760 0.3878520 0.5227299

Residual standard error:

lower est. upper

1.396448 1.616334 1.919055

Degrees of freedom: 80 total; 77 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.07 with 1 degrees of freedom. P = 0.301

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 20 7.58 7.600310 1.008 1.6168074 -0.0561792

2 3.9 20 3.13 3.062800 0.684 0.6583985 0.4564556

3 5.8 20 2.30 2.394199 0.438 0.5110875 -0.8242677

4 7.5 20 2.14 2.097906 0.595 0.4442432 0.4237541
```

BMD = 0.3608: BMDL = 0.3006

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3879 se: 0.05813

var=se^2: 0.003379

Per cent. of background at unit dose: 68

Per cent. of background at the highest dose: 5.5

ED50 (95% CI): 1.787 (1.332 , 2.397)

ln(Potency) -0.9471
se[log(Potency)]: 0.1499
se[log(Potency)]^2: 0.02246

PND 42 Offspring : Male : 46348201

DIMETHOATE:21-D:BRAIN:M:WHOLE
Thu Sep 09 14:28:41 2004
MRID: 46348201 Guideline: UNKNOWN
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)^g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 146.54770 156.07581 -69.27385

Coefficients:

Value Std.Error A 7.1404058 0.29424215 B 1.9809272 0.13223088

m 0.5895752 0.07318633

Correlation:

A B m A 1.0000000 0.1062892 0.3138343 B 0.1062892 1.0000000 0.8664410 m 0.3138343 0.8664410 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 6.5778893 7.1404058 7.7510267 B 1.7343709 1.9809272 2.2625336 m 0.4604572 0.5895752 0.7548995

Residual standard error: lower est. upper

1.139107 1.318471 1.565405

Degrees of freedom: 80 total; 77 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 10.78 with 1 degrees of freedom. P = 0.00103

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 20 7.19 7.140406 0.629 1.3176255 0.1683269

2 2.9 20 2.75 2.914317 0.669 0.5242261 -1.4017756

3 4.4 20 2.62 2.366396 0.415 0.4329132 2.6198142

4 6.1 20 2.00 2.122411 0.333 0.3951855 -1.3852649
```

BMD = 0.2527: BMDL = 0.2144

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5896 se: 0.07319

var=se^2: 0.005356

Per cent. of background at unit dose: 55

Per cent. of background at the highest dose: 2.7

ED50 (95% CI): 1.176 (0.9218 , 1.5)

ln(Potency) -0.5284
se[log(Potency)]: 0.1241
se[log(Potency)]^2: 0.01541

Day 224 F0 Adults : Female : 42251501

DIMETHOATE:224-D:BRAIN:F:WHOLE
Thu Aug 26 20:41:51 2004
MRID: 42251501 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 228.3252 239.1992 -110.1626

Coefficients:

Value Std.Error

A 6.0719227 0.1314300

в 2.0966338 0.1005747

m 0.5506869 0.0683010

Correlation:

A B

A 1.0000000 0.2560419 0.4941034

B 0.2560419 1.0000000 0.7508411

m 0.4941034 0.7508411 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 5.8169413 6.0719227 6.3380810

B 1.9064805 2.0966338 2.3057529

m 0.4306714 0.5506869 0.7041471

Residual standard error:

lower est. upper

0.8224906 0.9314216 1.0738743

Degrees of freedom: 112 total; 109 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.226 with 1 degrees of freedom. P = 0.268

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.00 28 5.94 6.071923 0.663 0.9386286 -0.743711812

2 0.09 28 6.02 5.879703 0.743 0.9092383 0.816488596

3 1.30 28 4.03 4.039578 0.656 0.6266899 -0.080872575

4 6.04 28 2.24 2.239471 0.455 0.3460104 0.008094143
```

BMD = 0.301: BMDL = 0.2542

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5507

se: 0.0683

var=se^2: 0.004665

Per cent. of background at unit dose: 58

Per cent. of background at the highest dose: 3.6

ED50 (95% CI): 1.259 (0.9871 , 1.605)

ln(Potency) -0.5966
se[log(Potency)]: 0.124
se[log(Potency)]^2: 0.01538

Day 224 F0 Adults : Male : 42251501

DIMETHOATE:224-D:BRAIN:M:WHOLE
Thu Aug 26 20:41:59 2004
MRID: 42251501 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 296.6609 304.8164 -145.3304

Coefficients:

Value Std.Error A 5.8136103 0.138919450 m 0.1476736 0.007752962

Correlation:

A 1.0000000 0.6002978 m 0.6002978 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 5.5447215 5.8136103 6.0955388 m 0.1330814 0.1476736 0.1638659

Residual standard error: lower est. upper 1.052030 1.190729 1.371887

Degrees of freedom: 112 total; 110 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.3875 with 2 degrees of freedom. P = 0.824

dose n chei Expected sd Exp.SD X2 Resid. 1 0.00 28 5.89 5.813610 0.730 1.1745112 0.34415709

BMD Computation

BMD = 0.7135: BMDL = 0.6568

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1477 se: 0.007753

var=se^2: 6.011e-05

Per cent. of background at unit dose: 86

Per cent. of background at the highest dose: 41

ED50 (95% CI): 4.694 (4.235 , 5.202)

ln(Potency) -1.913

se[log(Potency)]: 0.0525
se[log(Potency)]^2: 0.002756

Day 308 F1 Adults : Female : 42251501

DIMETHOATE:308-D:BRAIN:F:WHOLE
Thu Aug 26 21:05:40 2004
MRID: 42251501 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 257.9888 268.2462 -124.9944

Coefficients:

Value Std.Error

A 6.7556432 0.20376410

B 1.3648833 0.35281026

m 0.3620964 0.08279511

Correlation:

В

A 1.0000000 0.4587784 0.5496875

В 0.4587784 1.0000000 0.9636699

m 0.5496875 0.9636699 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 6.3628877 6.7556432 7.1726419

B 0.8168962 1.3648833 2.2804691

m 0.2299466 0.3620964 0.5701923

Residual standard error:

lower est. upper

1.179171 1.348190 1.574217

Degrees of freedom: 96 total; 93 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.01891 with 1 degrees of freedom. P = 0.89

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.00 24 6.73 6.755643 0.988 1.3531631 -0.0928384613

2 0.09 24 6.61 6.582797 0.848 1.3185947 0.1010666155

3 1.30 24 4.73 4.731678 0.801 0.9482011 -0.0086682673

4 6.04 24 1.97 1.969975 0.609 0.3945617 0.0003132394
```

BMD = 0.3698: BMDL = 0.2901

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.3621

se: 0.0828

var=se^2: 0.006855

Per cent. of background at unit dose: 70

Per cent. of background at the highest dose: 11

ED50 (95% CI): 1.914 (1.223 , 2.997)

ln(Potency) -1.016

se[log(Potency)]: 0.2287
se[log(Potency)]^2: 0.05228

Day 308 F1 Adults : Male : 42251501

DIMETHOATE:308-D:BRAIN:M:WHOLE
Thu Aug 26 21:05:46 2004
MRID: 42251501 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 349.7483 360.0057 -170.8741

Coefficients:

Value Std.Error A 8.1030954 0.3089928 B 2.7575841 0.3192727

m 0.4705517 0.1225254

Correlation:

A B m A 1.0000000 0.333130 0.5087436 B 0.3331300 1.000000 0.8531240 m 0.5087436 0.853124 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 7.5121535 8.1030954 8.7405237 B 2.1911776 2.7575841 3.4704033 m 0.2805718 0.4705517 0.7891703

Residual standard error:

lower est. upper 1.796324 2.053804 2.398129

Degrees of freedom: 96 total; 93 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.6898 with 1 degrees of freedom. P = 0.406

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.00 24 7.87 8.103095 1.527 2.044994 -0.558402534

2 0.09 24 8.13 7.881441 1.630 1.989787 0.611966412

3 1.30 24 5.64 5.657089 1.365 1.433195 -0.058413586

4 6.04 24 3.07 3.069234 1.061 0.774274 0.004847639
```

BMD = 0.3494: BMDL = 0.2565

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.4706

se: 0.1225

var=se^2: 0.01501

Per cent. of background at unit dose: 62

Per cent. of background at the highest dose: 5.8

ED50 (95% CI): 1.473 (0.8842 , 2.454)

ln(Potency) -0.7538
se[log(Potency)]: 0.2604
se[log(Potency)]^2: 0.0678

Day 205 F0 Adults : Female : 46181001

DIMETHOATE:205-D:BRAIN:F:WHOLE
Fri Aug 27 14:46:53 2004
MRID: 46181001 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 211.2150 221.6356 -101.6075

Coefficients:

Value Std.Error A 2.6039374 0.1571958

B 0.4116692 0.5460119

m 0.2831045 0.2061716

Correlation:

A B m A 1.0000000 0.6047972 0.6486768 B 0.6047972 1.0000000 0.9909277 m 0.6486768 0.9909277 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 2.30991302 2.6039374 2.935387 B 0.02960105 0.4116692 5.725188 m 0.06671544 0.2831045 1.201343

Residual standard error:

lower est. upper 0.8873267 1.0118743 1.1774163

Degrees of freedom: 100 total; 97 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 1.454 with 1 degrees of freedom. P = 0.228

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 25 2.46 2.6039374 0.79 0.9869187 -0.729225998

2 0.2 25 2.66 2.4832579 1.16 0.9434115 0.936718046

3 1.0 25 2.03 2.0634140 0.82 0.7904106 -0.211371320

4 6.5 25 0.76 0.7597772 0.25 0.2882539 0.003864346
```

BMD = 0.4466: BMDL = 0.2508

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.2831 se: 0.2062

var=se^2: 0.04251

Per cent. of background at unit dose: 75

Per cent. of background at the highest dose: 16

ED50 (95% CI): 2.448 (0.5875 , 10.2)

ln(Potency) -1.262

se[log(Potency)]: 0.7283
se[log(Potency)]^2: 0.5304

Day 205 F0 Adults : Male : 46181001

DIMETHOATE:205-D:BRAIN:M:WHOLE
Fri Aug 27 14:46:59 2004
MRID: 46181001 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 246.2969 256.7176 -119.1485

Coefficients:

Value Std.Error

A 2.3853419 0.1730838

В 1.0585396 0.1293070

m 0.5764393 0.3092732

Correlation:

A B 1

A 1.0000000 0.2712403 0.5940167

B 0.2712403 1.0000000 0.6492106

m 0.5940167 0.6492106 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 2.0654087 2.3853419 2.754833

B 0.8306425 1.0585396 1.348963

m 0.1987444 0.5764393 1.671907

Residual standard error:

lower est. upper

0.9335612 1.0645985 1.2387661

Degrees of freedom: 100 total; 97 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.0148 with 1 degrees of freedom. P = 0.903

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 25 2.37 2.385342 1.07 1.0707980 -0.071637814

2 0.2 25 2.26 2.240866 0.93 1.0064425 0.095058205

3 1.0 25 1.80 1.804064 0.74 0.8114026 -0.025042512

4 6.5 25 1.09 1.089841 0.57 0.4893233 0.001622017
```

BMD = 0.3438: BMDL = 0.1861

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.5764 se: 0.3093

var=se^2: 0.09565

Per cent. of background at unit dose: 56

Per cent. of background at the highest dose: 2.4

ED50 (95% CI): 1.202 (0.4201 , 3.442)

ln(Potency) -0.5509
se[log(Potency)]: 0.5365
se[log(Potency)]^2: 0.2879

Day 218 F1 Adults : Female : 46181001

DIMETHOATE: 218-D: PLASMA: F: WHOLE
Fri Aug 27 15:18:49 2004
MRID: 46181001 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 60.52336 68.27826 -27.26168

Coefficients:

Value Std.Error A 1.6264162 0.05694833 m 0.1766754 0.01017509

Correlation:

A m A 1.0000000 0.6019118 m 0.6019118 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.5172136 1.6264162 1.7434788 m 0.1575898 0.1766754 0.1980726

Residual standard error:

lower est. upper 0.4427904 0.5052632 0.5884226

Degrees of freedom: 98 total; 96 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 5.743 with 2 degrees of freedom. P = 0.0566

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 25 1.80 1.6264162 0.72 0.4615396 1.8804861

```
2 0.2 25 1.46 1.5699502 0.26 0.4443966 -1.2370725
3 1.0 24 1.30 1.3630210 0.23 0.3819601 -0.8083001
4 6.5 24 0.52 0.5158128 0.11 0.1348862 0.1520774
```

BMD Computation

BMD = 0.5964: BMDL = 0.5447

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1767 se: 0.01018

var=se^2: 0.0001035

Per cent. of background at unit dose: 84

Per cent. of background at the highest dose: 32

ED50 (95% CI): 3.923 (3.504 , 4.392)

ln(Potency) -1.733

se[log(Potency)]: 0.05759
se[log(Potency)]^2: 0.003317

Day 218 F1 Adults : Male : 46181001

DIMETHOATE:218-D:BRAIN:M:WHOLE
Fri Aug 27 15:18:54 2004
MRID: 46181001 Guideline: 83-4
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 113.80303 124.18351 -52.90151

Coefficients:

Value Std.Error

A 1.69172268 0.08610164

в 0.05990478 1.66100676

m 0.14397945 0.24666192

Correlation:

A B

A 1.0000000 0.6287968 0.6513526

B 0.6287968 1.0000000 0.9985784

m 0.6513526 0.9985784 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper

A 1.529162e+00 1.69172268 1.871565e+00

B 7.490659e-26 0.05990478 4.790743e+22

m 4.802066e-03 0.14397945 4.316909e+00

Residual standard error:

lower est. upper

 $0.4713238 \ 0.5378224 \ 0.6263406$

Degrees of freedom: 99 total; 96 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.03187 with 1 degrees of freedom. P = 0.858

```
dose n chei Expected sd Exp.SD X2 Resid.

1 0.0 25 1.68 1.6917227 0.45 0.5414192 -0.1082588226

2 0.2 25 1.66 1.6454031 0.63 0.5266886 0.1385720373

3 1.0 25 1.47 1.4729049 0.48 0.4717668 -0.0307878552

4 6.5 24 0.70 0.6999786 0.21 0.2240547 0.0004682722

BMD Computation
```

BMD = 0.7602: BMDL = 0.3695

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.144 se: 0.2467

var=se^2: 0.06084

Per cent. of background at unit dose: 87

Per cent. of background at the highest dose: 39

ED50 (95% CI): 4.814 (0.1676 , 138.3)

ln(Potency) -1.938
se[log(Potency)]: 1.713
se[log(Potency)]^2: 2.935

Day 28 Adults : Female : 46288001

DIMETHOATE: 29-D: BRAIN: F: WHOLE Thu Aug 26 21:28:09 2004

MRID: 46288001 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 31.61144 34.59864 -12.80572

Coefficients:

Value Std.Error A 2.6084883 0.22391809 m 0.1278757 0.01495178

Correlation:

A m A 1.0000000 0.6418415 m 0.6418415 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 2.1780355 2.6084883 3.1240130 m 0.1000239 0.1278757 0.1634828

Residual standard error:

lower est. upper 0.6927794 0.9168446 1.3558523

Degrees of freedom: 20 total; 18 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 9.644 with 2 degrees of freedom. P = 0.00805

dose n chei Expected sd Exp.SD X2 Resid.

BMD Computation

BMD = 0.8239: BMDL = 0.691

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1279 se: 0.01495

var=se^2: 0.0002236

Per cent. of background at unit dose: 88

Per cent. of background at the highest dose: 24

ED50 (95% CI): 5.42 (4.31 , 6.817)

ln(Potency) - 2.057

se[log(Potency)]: 0.1169
se[log(Potency)]^2: 0.01367

Day 28 Adults : Male : 46288001

DIMETHOATE: 29-D:BRAIN: M:WHOLE
Thu Aug 26 21:28:17 2004

MRID: 46288001 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 36.43884 39.42604 -15.21942

Coefficients:

Value Std.Error A 2.3427153 0.22699084 m 0.1057894 0.01833608

Correlation:

A m A 1.000000 0.635189 m 0.635189 1.000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.91123128 2.3427153 2.8716122 m 0.07350146 0.1057894 0.1522609

Residual standard error:

lower est. upper 0.5723182 0.7574228 1.1200954

Degrees of freedom: 20 total; 18 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.2449 with 2 degrees of freedom. P = 0.885

dose n chei Expected sd Exp.SD X2 Resid.

```
1 0.00 5 2.24 2.342715 0.69 0.7788405 -0.29489788
2 0.83 5 2.27 2.145785 0.66 0.7145351 0.38871879
3 2.48 5 1.78 1.802101 0.52 0.6020390 -0.08208481
4 10.38 5 0.78 0.781310 0.38 0.2651011 -0.01104942
```

BMD Computation

BMD = 0.9959: BMDL = 0.775

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.1058 se: 0.01834

var=se^2: 0.0003362

Per cent. of background at unit dose: 90

Per cent. of background at the highest dose: 33

ED50 (95% CI): 6.552 (4.665 , 9.203)

ln(Potency) -2.246

se[log(Potency)]: 0.1733
se[log(Potency)]^2: 0.03004

Day 1 Adults : Female : 45529702

DIMETHOATE:1-D:BRAIN:F:WHOLE Wed Aug 18 20:21:06 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 511.0838 515.4810 -252.5419

Coefficients:

Value Std.Error A 1.400226e+04 1.530550e+02 m 4.801487e-02 7.186638e-03

Correlation:

A m A 1.0000000 0.5913828 m 0.5913828 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.369314e+04 1.400226e+04 1.431835e+04 m 3.536891e-02 4.801487e-02 6.518233e-02

Residual standard error: lower est. upper 563.8050 705.5395 943.0758

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 2.517 with 2 degrees of freedom. P = 0.284

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 8 14150.00 14002.26 554.8488 698.0731 0.59861865

```
2 0.1 8 13625.00 13935.19 444.8114 694.7413 -1.26283056
3 0.5 8 13850.00 13670.10 687.1265 681.5724 0.74655058
4 3.0 8 12106.25 12123.84 826.5408 604.7383 -0.08228062
```

BMD Computation

BMD = 2.194: BMDL = 1.761

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.04801 se: 0.007187

var=se^2: 5.165e-05

Per cent. of background at unit dose: 95

Per cent. of background at the highest dose: 87

ED50 (95% CI): 14.44 (10.77 , 19.36)

ln(Potency) -3.036

se[log(Potency)]: 0.1497
se[log(Potency)]^2: 0.0224

Day 1 Adults : Male : 45529702

DIMETHOATE:1-D:BRAIN:M:WHOLE Wed Aug 18 20:21:12 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 515.1097 519.5069 -254.5549

Coefficients:

Value Std.Error A 1.365711e+04 161.84622769 m 3.992759e-02 0.00778649

Correlation:

A 1.0000000 0.5916283 m 0.5916283 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 1.3333055e+04 1.365711e+04 1.399168e+04 m 2.681049e-02 3.992759e-02 5.946226e-02

Residual standard error: lower est. upper 595.7456 745.5096 996.5029

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.4635 with 2 degrees of freedom. P = 0.793

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 8 13793.75 13657.11 247.0360 738.2140 0.52351076

```
2 0.1 8 13543.75 13602.69 802.4238 735.2619 -0.22674697
3 0.5 8 13293.75 13387.17 241.1838 723.5707 -0.36517900
4 3.0 8 12131.25 12115.41 1096.4024 654.5977 0.06846042
```

BMD Computation

BMD = 2.639: BMDL = 1.998

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.03993 se: 0.007786

var=se^2: 6.063e-05

Per cent. of background at unit dose: 96

Per cent. of background at the highest dose: 89

ED50 (95% CI): 17.36 (11.85 , 25.44)

ln(Potency) -3.221
se[log(Potency)]: 0.195
se[log(Potency)]^2: 0.03803

PND 11 Offspring : Female : 45529702

DIMETHOATE:1-D:BRAIN:F:WHOLE Wed Aug 18 20:02:45 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 474.3320 478.7292 -234.1660

Coefficients:

Value Std.Error A 6.328588e+03 87.826156540 m 6.888654e-02 0.009123527

Correlation:

A 1.0000000 0.5914097 m 0.5914097 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 6.151741e+03 6.328588e+03 6.510519e+03 m 5.256111e-02 6.888654e-02 9.028263e-02

Residual standard error:
lower est. upper
321.2198 401.9710 537.3039

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.4804 with 2 degrees of freedom. P = 0.786

dose n chei Expected sd Exp.SD X2 Resid.

```
1 0.0 8 6256.25 6328.588 195.3705 400.5716 -0.51077562
2 0.1 8 6350.00 6285.142 338.0617 397.8271 0.46111903
3 0.5 8 6125.00 6114.322 297.6095 387.0361 0.07803585
4 3.0 8 5143.75 5147.018 532.1369 325.9179 -0.02835973
```

BMD Computation

BMD = 1.529: BMDL = 1.256

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.06889

se: 0.009124

var=se^2: 8.324e-05

Per cent. of background at unit dose: 93

Per cent. of background at the highest dose: 81

ED50 (95% CI): 10.06 (7.762 , 13.04)

ln(Potency) - 2.675

se[log(Potency)]: 0.1324
se[log(Potency)]^2: 0.01754

PND 11 Offspring : Male : 45529702

DIMETHOATE:1-D:BRAIN:M:WHOLE Wed Aug 18 20:02:51 2004

MRID: 45529702 Guideline: NONGUIDELINE
Continuous Exponential Model (Decreasing)
Formula: chei = B + (A-B)*exp(-(m*dose)*g)

Variance Function: power

The BMD corresponds to a dose that results in a 10% reduction in the response relative to the control

Summary of Model Fitting Results

AIC BIC logLik 456.3905 460.7877 -225.1952

Coefficients:

Value Std.Error A 6.405480e+03 65.79821265 m 5.914452e-02 0.00674665

Correlation:

A m A 1.0000000 0.5917805 m 0.5917805 1.0000000

Approximate 95% confidence intervals

Coefficients:

lower est. upper A 6.272502e+03 6.405480e+03 6541.2770815 m 4.685327e-02 5.914452e-02 0.0746602

Residual standard error: lower est. upper 242.3740 303.3041 405.4186

Degrees of freedom: 32 total; 30 residual

Goodness of Fit

The chi-squared goodness-of-fit values should be taken as general indications of fit only. P-values are likely to be inaccurate to some degree

Pearson Chi-Square Statistic: 0.9782 with 2 degrees of freedom. P = 0.613

dose n chei Expected sd Exp.SD X2 Resid. 1 0.0 8 6475.00 6405.480 243.4866 300.1305 0.65515803 2 0.1 8 6362.50 6367.707 235.6602 298.3505 -0.04936043 3 0.5 8 6143.75 6218.829 359.9975 291.3355 -0.72890062 4 3.0 8 5375.00 5364.055 290.3200 251.0788 0.12329288

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BMD Computation

BMD = 1.781: BMDL = 1.5

Potency Measures

A unit dose (1 mg/kg) would result in 100*exp(-Potency)% of background activity

Potency: 0.05914 se: 0.006747

var=se^2: 4.552e-05

Per cent. of background at unit dose: 94

Per cent. of background at the highest dose: 84

ED50 (95% CI): 11.72 (9.372 , 14.66)

ln(Potency) -2.828

se[log(Potency)]: 0.1141
se[log(Potency)]^2: 0.01301